Human versus Analogue Insulin for Youth with Type 1 Diabetes in Low-Resource Settings: A Randomized Controlled Trial (HumAn-1 trial)

Protocol Number: 1

National Clinical Trial (NCT) Identified Number: TBD

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Sponsor: University of Pittsburgh

Funded by: The Leona M. and Harry B. Helmsley Charitable Trust

Version Number: 3.1

20 September 2022

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
	Decreased number of sensors from 6 to 2 starting at the 6 month f/u clinic visit	To make successful completion of all home visits (where sensors are changed and data scanned).
	Added language about Tanzania and Iraq	

Table of Contents

STATEMENT OF COMPLIANCE 1
1 PROTOCOL SUMMARY 1
1.1 Synopsis 1
1.2 Schema 2
1.3 Schedule of Activities (SoA) / Evaluations Calendar 3
2 INTRODUCTION 4
2.1 Study Rationale 4
2.2 Background 4
2.3 Risk/Benefit Assessment 5
2.3.1 Known Potential Risks 5
2.3.2 Known Potential Benefits 5
2.3.3 Assessment of Potential Risks and Benefits 5
3 OBJECTIVES AND ENDPOINTS 6
4 STUDY DESIGN 7
4.1 Overall Design 7
4.2 Scientific Rationale for Study Design 8
4.3 Justification for Dose 8
4.4 End of Study Definition 8
5 STUDY POPULATION 8
5.1 Inclusion Criteria 8
5.2 Exclusion Criteria 8
5.3 Lifestyle Considerations 9
5.4 Screen Failures 9
5.5 Strategies for Recruitment and Retention 9
6 STUDY INTERVENTION 10
6.1 Study Intervention(s) Administration 10
6.1.1 Study Intervention Description 10
6.1.2 Dosing and Administration 10
6.2 Preparation/Handling/Storage/Accountability 11
6.2.1 Acquisition and accountability 11
6.2.2 Formulation, Appearance, Packaging, and Labeling 11
6.2.3 Product Storage and Stability 11
6.2.4 Preparation 12
6.3 Measures to Minimize Bias: Randomization and Blinding 12
6.4 Study Intervention Compliance 12
6.5 Concomitant Therapy 12
6.5.1 Rescue Medicine 12
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 13
7.1 Discontinuation of Study Intervention 13
7.2 Participant Discontinuation/Withdrawal from the Study 13
7.3 Lost to Follow-Up 13
8 STUDY ASSESSMENTS AND PROCEDURES 14
8.1 Efficacy Assessments 14
8.2 Safety and Other Assessments 14
8.3 Adverse Events and Serious Adverse Events 15

8.3.1 Definition of Adverse Events (AE) 15
8.3.2 Definition of Serious Adverse Events (SAE) 16
8.3.3 Classification of an Adverse Event 16
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 17
8.3.5 Adverse Event Reporting 17
8.3.6 Serious Adverse Event Reporting 18
8.3.7 Reporting Events to Participants 18
8.3.8 Events of Special Interest 18
8.3.9 Reporting of Pregnancy 18
8.4 Unanticipated Problems 18
8.4.1 Definition of Unanticipated Problems (UP) 18
8.4.2 Unanticipated Problem Reporting 19
8.4.3 Reporting Unanticipated Problems to Participants 19
9 STATISTICAL CONSIDERATIONS 19
9.1 Statistical Hypotheses 19
9.2 Sample Size Determination 20
9.3 Populations for Analyses 21
9.4 Statistical Analyses 21
9.4.1 General Approach 21
9.4.2 Analysis of the Primary Efficacy Endpoint(s) 21
9.4.3 Analysis of the Secondary Endpoint(s) 22
9.4.4 Safety Analyses 22
9.4.5 Baseline Descriptive Statistics 23
9.4.6 Planned Interim Analyses 23
9.4.7 Sub-Group Analyses 24
9.4.8 Tabulation of Individual participant Data 24
9.4.9 Exploratory Analyses 24
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 24
10.1 Regulatory, Ethical, and Study Oversight Considerations 24
10.1.1 Informed Consent Process 24
10.1.2 Study Discontinuation and Closure 25
10.1.3 Confidentiality and Privacy 25
10.1.4 Future Use of Stored Specimens and Data 25
10.1.5 Key Roles and Study Governance 25
10.1.6 Safety Oversight 26
10.1.7 Clinical Monitoring 27
10.1.8 Quality Assurance and Quality Control 27
10.1.9 Data Handling and Record Keeping 27
10.1.10 Protocol Deviations 28
10.1.11 Publication and Data Sharing Policy 29
10.1.12 Conflict of Interest Policy 29
10.2 Additional Considerations 29
10.3 Abbreviations 30
10.4 Protocol Amendment History 32
11 REFERENCES 34

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

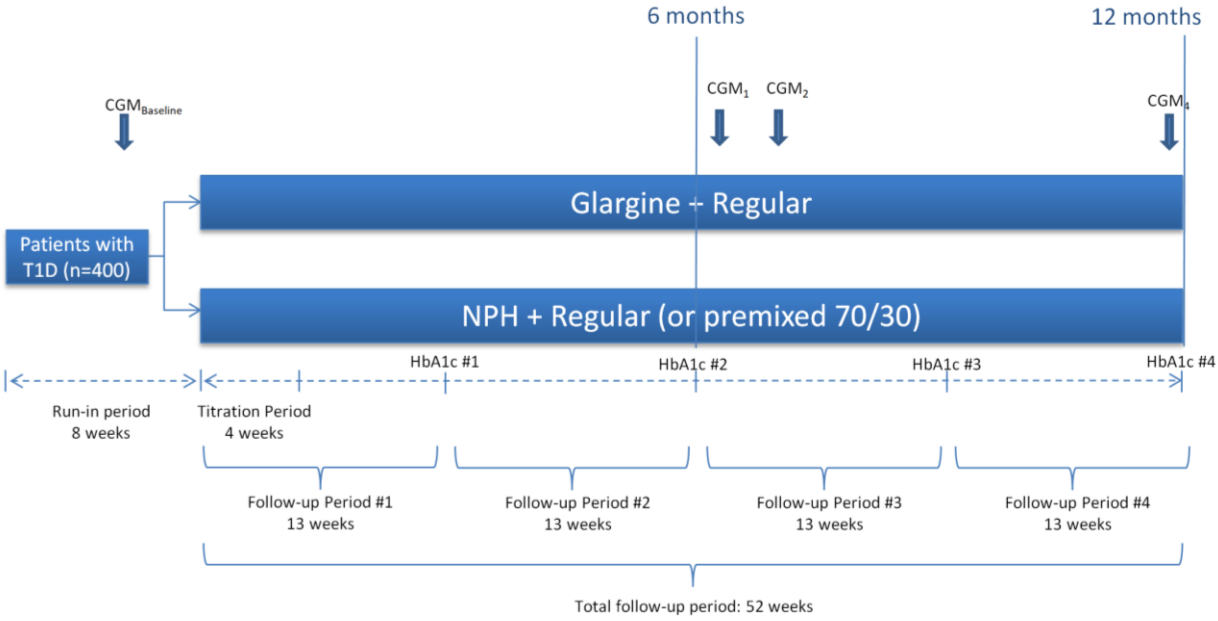
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the University of Pittsburgh Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Analogue vs Human Insulin for Youth with Type 1 Diabetes in Low-Resource Settings: A Randomized Controlled Trial (AnHuT1D trial)
Study Description:	The AnHuT1D trial is 1:1 randomized, parallel-group, open-label trial comparing insulin glargine, a basal insulin analogue, against human insulin (NPH or premixed 70/30) in youth living with type 1 diabetes (T1D) in low resource settings.
Objectives	Primary Objective: To determine whether insulin glargine reduces the risk of serious hypoglycemia or improves Time in Range over 3-6 months when compared against standard of care human insulin (e.g. NPH or premixed 70/30) among youth living with type 1 diabetes (T1D) in low resource settings.
Endpoints:	Co-Primary Endpoints: Time in serious hypoglycemia and Time in range
Study Population:	Youth living with type 1 diabetes (T1D) in low resource settings.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Bangladesh (Dhaka), Tanzania (Mwanza) and Iraq (Kirkuk province)
Description of Study Intervention:	Insulin glargine (a long-acting insulin analogue)
Study Duration:	3 Years
Participant Duration:	1 Year (12 months)

1.2 SCHEMA


6 months
12 months
CGM Baseline
CGM1
CGM2
CGM4
Glargine + Regular
Patients with T1D (n=400)
NPH + Regular (or premixed 70/30)
HbA1c #1
HbA1c #2
HbA1c #3
HbA1c #4
Run-in period 8 weeks
Titration Period 4 weeks
Follow-up Period #1 13 weeks
Follow-up Period #2 13 weeks
Follow-up Period #3 13 weeks
Follow-up Period #4 13 weeks
Total follow-up period: 52 weeks

1.3 SCHEDULE OF ACTIVITIES (SOA) / EVALUATIONS CALENDAR

Procedures	Screening Day -8 weeks to -1 Day	Enrollment/Baseline Visit 0, Day 1	Insulin Titration Phase Day +1 to +4 weeks	Clinic Visit 1 +3 months	Clinic Visit 2 +6 months	Home Visits* #1 and 2	Clinic Visit 3 +9 months	Home Visit #3 (2 weeks before final clinic visit)	Final clinic visit (4) +12 months
Confirm Eligibility	X								
Informed consent	X								
Demographics + Medical History	X								
Quality of Life Survey (e.g. PedsQL, ITSQ)	X				X				X
Baseline labs are drawn	X								
Baseline CGM placed (sensor #0)	X								
Scan and upload baseline CGM sensor data		X							
Baseline lab results and vitals		X							
Randomization		X							
Dispense glargine if randomized to intervention arm		X							
Dispense intranasal glucagon		X							
Provide in depth education and counseling		X							
Titrate insulin glargine or continue to adjust human insulin at home			X						
Draw HbA1c	X			X	X		X		X
CGM #1 placed					X				
Scan/upload CGM sensor data (i.e. CGM sensor #1, 2) and replace sensor if needed.						X			
Place CGM sensor #4								X	
Scan and upload data from sensor #4									X

*In some cases, scheduled “home visits” will actually be done in the clinic (i.e. another clinic visit), if requested by the participant or for security concerns (as in the case of Iraq).

2 INTRODUCTION

2.1 STUDY RATIONALE

Long-acting insulin analogues have become a de-facto standard of care for patients with T1D living in high-income countries. Unfortunately, insulin analogues remain unavailable or unaffordable for much of the global population. In both 2017 and 2019, applications to add long-acting insulin analogues to the WHO's Model List of Essential Medicines (EML) were rejected due to insufficient evidence of superiority and an unfavorable cost-effectiveness profile when compared against older, less expensive, human insulins (e.g., NPH insulin and premixed 70/30 insulin). In 2021, long-acting insulin analogues were added to the EML but the decision remains controversial since the WHO concluded that "magnitude of clinical benefit of long-acting insulin analogues over human insulin for most clinical outcomes was small." Moreover, studies that compare long-acting insulin analogues versus human insulins conducted in high-income settings may not generalize to children and young adults living with T1D in very low-resource settings.

To address this unmet need, Pitt has partnered with BWH and Life for a Child to conduct a randomized controlled trial comparing insulin glargine, a long-acting analogue insulin, against human insulin among 400 children and young adults living with T1D in a lower resource setting (initial clinical sites planned in Bangladesh and Tanzania; potential to add sites in Iraq or other LMICs as trial progresses).

2.2 BACKGROUND

This proposal addresses an important unmet clinical need by generating rigorous evidence on the comparative clinical benefits, risks, quality of life and cost-effectiveness of a long-acting insulin analogue vs. intermediate-acting human insulin in low-resource settings. Prior studies conducted in higher income settings are not sufficient because they do not address this specific population(s) of interest and have also not used continuous glucose monitoring (CGM) to capture important glycemic outcomes.

In low-resource or humanitarian settings where glycemic control is typically poor and food insecurity is common, long-acting insulin analogues may offer tangible clinical benefits for patients with T1D. NPH insulin must be dosed at least twice daily in individuals with T1D to ensure 24-hour basal insulin coverage and peaks 4-6 hours after injection, which can lead to hypoglycemia if not eating or overnight. Premixed 70/30 human insulin contains a mix of 70% NPH insulin and 30% short-acting regular insulin, which has been associated with a significant hypoglycemia risk. Glargine has a duration of 24 hours, can be injected once a day, and has a smoother time-action profile. In settings of food insecurity, the pharmacokinetic profile of glargine may reduce the risk of severe hypoglycemic events overnight, which can be fatal. Moreover, it may reduce potential long-term sequalae of recurrent hypoglycemia, such as hypoglycemia unawareness, and may allow for improved glycemic control thereby reducing the risk of long-term complications (e.g., microvascular disease) from diabetes.

Existing efforts to overcome a two-tiered system of global diabetes care (i.e. access to modern, designer insulin analogues in high-income settings, but only human insulins for much of the world's poor) are currently hampered by a lack of hard evidence. Although conclusive evidence for the clinical superiority of insulin analogues in these settings is lacking, many patients and global advocates strongly prefer newer insulins. This is due in part to their added convenience and reduced risk of hypoglycemic events

(especially overnight) when compared against human insulins (Pedersen-Bjergaard et al., The Lancet Diabetes & Endocrinology 2014). In fact, existing WHO treatment guidelines recommend considering long-acting insulin analogues in cases where patients experience recurrent episodes of hypoglycemia on human insulin (Roglic & Norris, Annals of Internal Medicine 2018).

The landscape of global access to medicine for patients living with insulin-dependent diabetes is undergoing a dramatic transformation. Clinics in low-resource settings supported by Life for a Child will soon begin transitioning some children and young adults with T1D from usual care with human NPH insulin to insulin glargine (Basaglar; Lilly/Boehringer Ingelheim). Given these changes, and existing gaps in the evidence, this is an opportune time to conduct a rigorous study that directly compares long-acting insulin analogues vs. human insulins (e.g., NPH or premixed 70/30 insulin) in low-resource settings. The overall goal of this project is to generate high-quality evidence on the potential clinical benefits and comparative cost-effectiveness of long-acting insulin analogues versus standard-of-care human insulin for patients living with T1D in these settings.

We will achieve this by conducting a randomized trial comparing glargine, a long-acting insulin analogue, against human NPH insulin or premixed 70/30 human insulin among 400 children and young adults living with T1D in lower resourced settings.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Discomfort, inconvenience, or stigma of wearing a CGM sensor
Low blood sugar due to change in insulin regimen

2.3.2 KNOWN POTENTIAL BENEFITS

Subjects may increase knowledge of diabetes management and experience improvements in blood glucose control (although this cannot be guaranteed). They may find out what type of insulin is better for management of their blood sugars and reduce the risk of having low blood sugar events. Participants will receive compensation (and/or transportation reimbursement) for their time participating in the study and in addition, will be provided with no-cost laboratory studies and a nasal spray medication called glucagon to help manage severe hypoglycemic events, should they occur.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

CGM sensors: subjects will be advised to clean the area of the skin prior to placement. Study staff will use typical hygiene procedures to clean the area prior to sensor replacement. The devices are small (size of two stacked quarters) and can be covered up by a shirt sleeve. The sensors are silent - they do not beep, make noise, or emit light. The sensors can be worn while bathing, swimming or while the participant is engaged in physical activities. We will advise participants to take extra care while removing clothing or while drying off. During especially intense physical activity, we will also advise participants to cover the sensor with an additional layer of protection (e.g. transparent dressing or elastic wrap).

Low blood sugar (hypoglycemia): Use of any insulin (including the standard of care human insulins) confers the risk of experiencing hypoglycemia. This risk already exists for all study participants. Most mild cases can be managed by taking in food or beverages that contain sugar (e.g. having some candies

or juice available). Insulin glargine has been shown to reduce the risk of hypoglycemia in some settings and patient populations. In addition, the protocol specifies that the insulin titration will be conservative - namely that subjects will start with a lower dose of insulin glargine than their previous total basal insulin dose. Study personnel will be available via a dedicated study phone number (or via SMS) should hypoglycemia occur. Further, all participants will be provided with an intranasal medication called glucagon that can be used as a rescue medication in cases of severe and life-threatening hypoglycemic events. These events are expected to be rare.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether insulin glargine reduces the risk of serious hypoglycemia or improves glycemic Time in Range (TIR) at 6 months when compared against standard of care human insulin (e.g. NPH or premixed 70/30)	The coprimary outcomes for this trial are 1) percent time-in-serious-hypoglycemia (<54 mg/dl) and 2) percent time-in-range (70-180mg/dl).	We selected these coprimary outcomes after consulting international experts and reviewing international consensus guidelines. Even though level 2 hypoglycemic events (i.e. <54mg/dl) are less common than milder, level 1 events (i.e. <70mg/dl), they are far more likely to be clinically significant. Experts also provided feedback that it was important to assess efficacy on both hypoglycemia and time-in-range (increasingly accepted among clinicians as a valid surrogate endpoint by itself since durable increases in TIR are likely strongly associated with good glycemic control and therefore a reduction in the risk of microvascular complications of type 1 diabetes), since a

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		benefit on either of these two outcomes will be useful clinical knowledge.
Secondary		
To determine whether insulin glargine improves glycemic control when compared against standard of care human insulin (e.g. NPH or premixed 70/30)	HbA1c (%)	HbA1c is a widely accepted surrogate for glycemic control and currently serve as treatment targets recommended by several professional societies, including the ADA/EASD, ACP and others.

Ascertainment of the Primary Outcome: Patients will be followed from the start of randomization (day 0) up through +12 months. At every 3 months, study participants will return to clinic for routine follow-up (including insulin refills) and HbA1c testing, as is currently the standard of care.

Blinded CGM sensors (duration=14 days each) will be placed on every study participant according to following schedule: (1) One baseline sensor during the run-in phase (i.e. before randomization), (2) two back-to-back sensors at 6 months after randomization and (3) one sensor at the final 2 weeks of the study (during month 12), to assess durability of CGM results.

Secondary outcomes will include: Time-in-hypoglycemia (<70mg/dl), time-above-range (either >180mg/dl or >250mg/dl), and number nocturnal hypoglycemic events (1200-0600h). We will also measure and compare overall glycemic control (HbA1c), the rate of severe hypoglycemic events (requiring the external assistance of another party), and the rate of symptomatic hypoglycemic events reported by clinical history, rate of diabetic ketoacidosis (measured by self-report and confirmed through review of hospital records) and overall mortality (all cause death). We will also explore durability of treatment effects by comparing % time <54mg/dl during the final 2 weeks of the 1-year follow-up.

4 STUDY DESIGN

4.1 OVERALL DESIGN

HumAn-1 is a randomized, placebo-controlled, parallel group (1:1 allocation ratio), open-label, multi-site RCT that compares insulin glargine against NPH or premixed 70/30 among youth with type 1 diabetes in low resource settings.

Justification for open-label nature of trial: it is not practical and would be very challenging in a low resource setting to administer the appropriate matching placebos. For example, NPH may be dosed twice a day whereas insulin glargine is typically dosed only once daily. NPH is a cloudy liquid where glargine is clear (transparent). Furthermore, the formulations that will be employed in this study differ.

Specifically, both forms of human insulin, (NPH or premixed 70/30) are supplied in glass vials, whereas the donated insulin glargine used in this study will be supplied as a pre-filled cartridge. Due to availability and procurement related reasons, the MSF Iraq site will only use pre-filled, disposable pens for both the analogue and human insulins used.

We do not expect the lack of blinding to impact the primary outcome(s) because of two reasons: 1) percent time-in-range and time-in-hypoglycemia are not patient-reported outcomes, and 2) they will be obtained from professional (blinded) CGM sensors. As stated before, participants will not be able to view their own daily glucose readings since the CGM sensors used in this study (Abbott Freestyle Libre Pro) can only be read by dedicated Reader devices which are in the sole possession of study staff. If study participants would like, they may view their CGM sensor data at the conclusion of the study (i.e. when she or he has completed the final study visit and all study related procedures).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

NPH or premixed 70/30 is an appropriate control given that this is the current standard of care for the vast majority (over 90%) of youth living with T1D in low resource settings.

4.3 JUSTIFICATION FOR DOSE

There is no fixed or target insulin dose for either the intervention or usual care treatment arms. Rather, insulin will be titrated by each participants' treating clinician according to local standard of care and treatment practices.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Children and young adults (age 7-25)
2. Have a clinical diagnosis of type 1 diabetes (T1D)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior use of any insulin analogue
2. Patients (or parents for children <18 years old) who refuse to or cannot provide informed consent

3. Who are currently pregnant or plan to become pregnant over the next year
4. Who have previously used a continuous glucose monitor (CGM) for glucose monitoring
5. Who were first diagnosed with T1D less than 12 months ago
6. Who is diagnosed with severe malnutrition

The rationale for selecting this patient population is threefold: (1) they comprise most of the individuals living with T1D in the settings that Life for a Child (LFAC) supports and where we hope to conduct the trial, (2) it will be difficult to ensure that CGM sensors are not accidentally removed prior to the end of each 14-day measurement period for children under 7 years of age, and (3) this patient population is likely the group that will be treated first with analogue insulins if/when such products are more widely procured globally.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

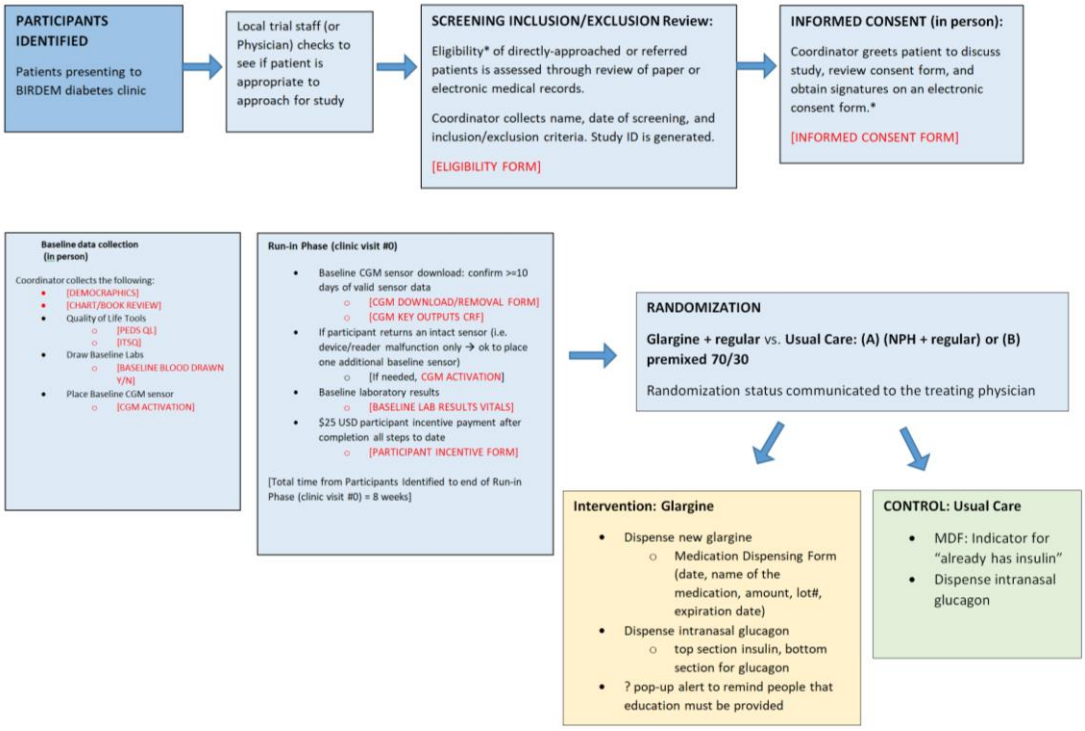
5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor (e.g. were recently diagnosed with type 1 diabetes) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients with T1D and their parents or guardians (if under 18 years old) will be approached by local study staff or will be referred by their physicians as they present for routine clinical care at diabetes centers within each trial site. We will use a convenience sampling approach, akin to first-come first-served. The rationale for this sampling approach is twofold: 1) this approach best mimics real world clinical practice and 2) may be easiest to operationalize.

For example, at the large urban diabetes hospital in Dhaka, Bangladesh (BIRDEM), potential participants will be approached as they present for diabetes follow-up at the large outpatient pediatric diabetes clinic. They will then be presented with information, in their local language, about the study. Those who meet all inclusion or exclusion criteria and who provide consent (or in some cases, assent) will be enrolled in the study. See Figure below.



6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Insulin glargine (intervention)
Human insulin (control)

6.1.2 DOSING AND ADMINISTRATION

Intervention (glargine)
Formulation: Available as a clear liquid in a glass cartridge (1 cartridge =3ml=300 units).
Route: Subcutaneous injection using insulin syringe and needle. At the site in Iraq, glargine will be available only as a prefilled, disposable pen (1 pen = 3ml = 300 units).
Amount of each dose: varies depending on baseline basal insulin needs
Dose escalation scheme: Participants randomly assigned to glargine will start with a dose that is generally equal to 80% of their total basal human insulin dose prior to the switch (per ISPAD guidelines and the switching guide developed by Life for a Child with the guidance of Dr. Ragnar Hanas and two other ISPAD members familiar with less-resourced settings).
Frequency of dose: once per day (usually administered before bedtime)
Duration of therapy: 12 months

The rationale for not using insulin pens is to ensure that any clinical differences which may be reported are due to differences in the medications alone, not due to a combination of a newer medication and a more convenient delivery device (i.e. a prefilled disposable insulin pen)

Control (human insulin)
Drug: NPH or Premixed 70/30
Formulation: Available as a liquid in a glass vial or glass cartridge (10ml=1000IU). At the site in Iraq, NPH will be available only as a prefilled, disposable pen (1 pen = 3ml = 300 units).
Route: Subcutaneous injection using insulin syringe and needle
Amount of each dose: varies depending on baseline basal insulin needs (per usual care or treating clinician)
Frequency of dose: once or twice per day (per usual care or treating clinician)
Duration of therapy: 12 months

After random treatment assignment, all participants will enter a 4 week titration phase. During this phase, participants randomly assigned to human insulin will continue their usual care, however they will receive the same frequency of blood glucose testing and the same intensity of education and counseling as those randomized to glargine (e.g. titration advice according to fasting glucose targets and strategies to avoid hypoglycemia). Specifically, participants in both groups will have equal access to test strips (sufficient to test up to 5 times per day during the active titration phase and thereafter 3 times per day).

Both treatment arms will subsequently titrate their assigned basal insulin dosage according to a fasting glucose target set according to local practice patterns (as recommended by LFAC). We will not recommend aggressive lowering of fasting glucose levels or HbA1c, because prior studies show that the rate of severe hypoglycemia is common in these settings.

Participant compliance will be measured at each clinic and/or home visit using case report forms.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

All insulins, test strips, glucometers will be supplied to the investigator as a donation from the Australian based non-profit humanitarian organization Life for a Child. Medications and supplies in Iraq will be supplied by Médecins Sans Frontières (MSF), an international humanitarian and crisis relief organization.

Medications and CGMs will be securely stored at the clinical or medical supply distribution facilities of the BIRDEM hospital located in Dhaka Bangladesh, the Tanzanian Diabetes Association in Dar Es Salaam, Tanzania, or at MSF Iraq.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

See 6.1.2 above

6.2.3 PRODUCT STORAGE AND STABILITY

For longer term storage, insulin should be kept below 25 degrees C, or per package insert instructions.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization: We will use a stratified blocked randomization approach with variable block sizes. Since we aim to conduct a multi-center trial, we will stratify randomization by center, since there will likely be differences in the patient population or clinical practice patterns at each center that may affect the outcome. For example, stratifying randomization by center may also help to protect against imbalances in the distribution of participants who use NPH or 70/30 at baseline, as these choices may reflect local (i.e. center-specific) practice patterns.

The randomization sequence will be prepared in advance by the lead statistician, Dr. Andrew Althouse, and integrated into an online, secure, data management system that will be developed specifically for this trial. Dr. Althouse will use the ”blockrand” package in R statistical software to generate the randomization sequence.

Allocation concealment: Local trial staff will use the online data management system developed for this trial to obtain the next randomization sequence. Neither the PI nor the local trial staff will have access to the randomization sequence. Treatment assignment will only occur after a study participant has been determined to meet all inclusion and exclusion criteria (i.e. screening) and completed the baseline study procedures in the run-in phase.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to both study interventions and use of CGMs will be assessed at each home and clinic visit using electronic case report forms.

We will measure adherence to the study interventions by asking each participant during all clinic and home visits what type(s) of insulin they are currently using. To monitor adherence, staff will also ask how many units of each insulin and total insulin dose (if participant is using more than 1 type of insulin) the participant takes per day during all clinic and home visits. To confirm adherence, staff will ask to see the participant’s insulin vials or cartridges.

Use of CGMs and any potential sensor malfunctions will be directly assessed in person (or by telephone) by local trial staff.

6.5 CONCOMITANT THERAPY

We will also assess whether any non-study insulin analogues have been introduced or used by any participant during follow-up.

6.5.1 RESCUE MEDICINE

The study site will/supply intranasal glucagon (Bangladesh and Tanzania) or premixed injectable glucagon (MSF Iraq) as a rescue medication that will be provided by the sponsor to all participants. If we cannot successfully import glucagon due to lack of device registration in country or difficulty in clearing customs, we will aim to provide all participants access to injectable glucagon in the form of an emergency kit (available on the WHO's Model List of Essential Medicines). The use of rescue medications is allowable at any time during the study. Training on use of the nasal spray or injectable kit will also be provided at the time of dispensing. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. For example, a participant may decide that they would like to go back to their previously used human insulin regimen. During the study, participants will be encouraged to stay on their randomly assigned treatment group, unless there is a clinical reason to switch (i.e. cross-over).

At the end of this study, participants will be given the opportunity to switch to the contralateral treatment group if they would like to (and the treating provider agrees).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon written request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention (e.g. did not receive their randomly assigned medication) may be replaced. Subjects who sign the informed consent form, and are randomized and *receive* the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled clinic visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

See primary outcome.

8.2 SAFETY AND OTHER ASSESSMENTS

Study Measurements

Baseline demographics/comorbidities	**Description**
Age	At time of randomization, in years
Duration of type 1 diabetes	Based on self-report or extraction from medical record, in years
Type of insulin regimen	Generally, as two categories, NPH + regular (basal/bolus regimen) or premixed 70/30
Number of units of insulin per day	Total number of international units of insulin used per day, including all basal and bolus insulins.
Mean HbA1c (%) [SD]	HbA1c laboratory result (units=%), most recent
Complications of Type 1 Diabetes	Clinical presence or absence of diabetic retinopathy, neuropathy, or nephropathy (extracted from medical record)
Hypoglycemic events	Number of episodes of symptomatic hypoglycemic events in the past 12 months
Co-Primary Outcomes:	
Time-in-serious hypoglycemia	% spent less than 54mg/dl, averaged across all daily measures averaged across two CGM sensors starting 6 months after randomization
Time-in-range (TIR)	% between 70 and 180mg/dl inclusive, averaged across two CGM sensors 6 months after

	randomization
Secondary Outcomes:	
Time-in-hypoglycemia	% spent less than 70mg/dl
Time-above-range	% spent greater than 180mg/dl
Nocturnal hypoglycemic events	Number of events (defined as >=15mins in duration < 70mg/dl) between 1200 and 0600
Glycemic control (HbA1c)	Mean HbA1c lab result at baseline, 3, 6, 9 and 12 months after randomization
Rate of severe hypoglycemic events	Events requiring the assistance of an external third party person
Rate of diabetic ketoacidosis (DKA)	Measured by self-report and confirmed through review of hospital records
Quality of Life (e.g. Fear of Hypoglycemia Survey)	As assessed using validated instruments (PedsQL and Insulin Treatment Satisfaction Questionaire (ITSQ)).
Adverse Events	
Hypoglycemic events (clinically significant events)	See primary and secondary outcomes above. Insulin in any form is known to be associated with low blood sugars. Therefore, we are measuring this as a primary/secondary outcome…but it also may be considered an adverse event/safety event.
Severe hypoglycemic events (<54mg/dl by CGM) > 10%	In the case severe hypoglycemia exceeds 10% on any CGM sensor, the treating clinician will be notified.
Skin discomfort/irritation	Self-report
Skin infection	Self-report
Mortality	All-cause mortality, assessed by 3rd-party voluntary report to study staff and/or during failed attempts to follow-up with a trial participant
All other adverse events	Will be assessed periodically and categorized according to established procedures and taxonomy.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

The local site PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's baseline condition deteriorates at any time during the study, it may be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The local trial coordinator or research assistant will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Non-serious AE will be recorded in the study database and will be summarized (by treatment arm) in safety reports for the DSMB to discuss at regular meetings.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not Applicable.

8.3.9 REPORTING OF PREGNANCY

If a participant becomes pregnant or decides to try and get pregnant during the study (i.e. changes their mind or has an unplanned pregnancy), the participant should inform the local trial staff and local site PI immediately. Since this is one of the main exclusion criteria, these participants would then drop out of the study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 2 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not Applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Null hypothesis: % Time-in-serious hypoglycemia and % Time in Range (TIR) in the insulin glargine group is the same as % Time-in-serious hypoglycemia and % TIR in the control group (usual care with human insulin).

Alternative hypothesis: % Time-in-serious hypoglycemia or % TIR in the insulin glargine group is different than in the control group (usual care with human insulin).

Since this trial has 2 coprimary outcomes, a win on either outcome will be considered to be a positive trial. For example, if insulin glargine "wins" ($p<0.025$ for benefit) on either the Time-in-serious hypoglycemia OR TIR outcome, it's considered a positive trial for analogue insulin.

9.2 SAMPLE SIZE DETERMINATION

We estimated power using a bootstrap-resampling approach due to the expected non-standard distribution of the outcome variables (i.e. %time in serious hypoglycemia and %time-in-range). Using individual patient level CGM data collected from a pilot study involving more than 80 children with T1D in Uganda and Kenya (personal communication Professor Antoinette Moran, University of Minnesota), we calculated a mean percent time<54 mg/dl of 5.8, standard deviation of 6.6, a maximum of 24. We next assumed a clinically meaningful 33% relative reduction in percent time-in-serious-hypoglycemia (e.g., from a median of 6% to 4%) since clinical guidelines3 recommend that patients and providers aim for <15 minutes per day (~1%) in hypoglycemia spent at <54 mg/dl. Therefore, in each simulated trial, the simulated patients in the usual-care arm had an outcome drawn from the "control" distribution; the simulated patients in the glargine arm had an outcome drawn from the control distribution multiplied by 0.67 (e.g. corresponding to a 33% relative reduction in time-in-serious-hypoglycemia).

To estimate the study power, we simulated outcomes for control-group (human insulin) and treatment-group (analogue insulin) at sample sizes ranging from 100 up to 400 patients and performed the planned primary analyses described above on the simulated datasets. The power to detect a treatment benefit of glargine insulin is thereby computed as the percentage of simulated trials with a p-value less than 0.025 favoring glargine on each of the respective coprimary outcomes. Since we have 2 coprimary outcomes, an alpha threshold of 0.025 is used for each analysis to control the overall trial-wide type 1 error probability at 0.05. Using this approach, an analytic sample size of 300 patients (150 per arm) would have 77.7% power to detect a treatment benefit corresponding to approximately a 33% relative reduction in time-in-serious-hypoglycemia. If the benefit is larger (e.g. 50% relative reduction) we will have over 99% power to detect a treatment benefit on the hypoglycemia endpoint.

For the time-in-range endpoint, we used an absolute increase rather than a relative decrease; this is because of the different distribution of time-in-range as opposed to time-in-serious-hypoglycemia (which has a large clustering of values in single digits). The pilot data showed a mean time-in-range of 27 with a standard deviation of 17; most values ranged between about 10 and 70; we felt that a 10% absolute increase in time-in-range would be a clinically meaningful improvement. Using a similar resampling-based approach described above, for this endpoint simulated patients in the usual care arm had an outcome drawn from the "control" distribution; simulated patients in the analogue arm had an outcome drawn from the control distribution plus 10 (corresponding to a 10% absolute increase in the time-in-range endpoint). The planned sample size of N=300 retains excellent power (>99%) for a 10% absolute improvement in time-in-range.

Table. Power For "%Time<54mg/dl" and "%Time-In-Range" Outcomes At Various Sample Sizes (alpha=0.025)

Sample Size	%Time<54mg/dl		%Time-In-Range
	33% Relative Decrease	50% Relative Decrease	10% Absolute Increase
N=200	56.2%	96.6%	97.5%
N=250	64.3%	99.0%	99.5%
N=300	77.7%	99.8%	>99.9%

Therefore, we believe that a sample size of N=300 patients (150 per group) with analyzable outcome data will be sufficient to have sufficient power for clinically relevant effects on the co-primary outcomes of time-in-serious-hypoglycemia (77.7% power to detect a 33% relative decrease at alpha=0.025) and

time-in-range (>99% power to detect a 10% absolute increase at alpha=0.025). This analytic strategy allows the trial to conclude as a positive trial if glargine demonstrates a benefit on either the time-in-serious-hypoglycemia endpoint or the time-in-range endpoint. Splitting the alpha to use 0.025 for each coprimary endpoint controls the overall trial-wide error at 0.05; this gives the opportunity to test both endpoints, which is important as knowledge of a benefit on either aspect of glycemic control is useful to inform clinical practice.

9.3 POPULATIONS FOR ANALYSES

Intention-to-treat (ITT) Analysis Dataset (i.e. all randomized participants)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Not Applicable

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The trial will have coprimary outcomes. The first of these will be percent time-in-serious-hypoglycemia (<54 mg/dl) as described above, which will be recorded as a continuous variable theoretically ranging from 0 (no time spent in serious hypoglycemia) to 100 (all time spent in serious hypoglycemia); the realistic range for this outcome is ~0 to 25, as described below. Data on percent time in hypoglycemia will be downloaded from individual CGM sensors and then pooled across all sensors collected during the intensive CGM phase (month +3 to +6) to compute a single value for “time in serious hypoglycemia” for each patient. The primary analysis will be performed using a multivariable linear regression model where treatment assignment is the primary fixed effect of interest, with age, study site, and time-in-serious-hypoglycemia and time-in-range from the baseline CGM (run-in phase, prior to initiation of study treatment) included as covariates. This approach will be used because adjustment for covariates known to be strongly associated with the outcome increases statistical power; including the baseline measurement as a covariate also provides a safeguard against random imbalances in individual level baseline risk of hypoglycemia (e.g. one arm having patients with more hypoglycemic tendencies than the other arm) introducing a bias in the estimated treatment effect.

The second coprimary outcome will be percent time-in-range (70-180 mg/dl). Likewise, this also will be recorded as a continuous variable theoretically ranging from 0 (no time spent in range) to 100 (all time spent in range). The realistic range for this outcome variable is about 10 to 70, based on pilot data also described below. Again, data from all CGM sensors collected during the intensive CGM phase will be pooled to compute a single value for “time in range” for each patient. The analytic approach used for this endpoint will mirror the approach used for the time-in-serious-hypoglycemia endpoint: a multivariable linear regression model where treatment assignment is the primary fixed effect of interest, with age, study site, and time-in-range from the baseline CGM (run-in phase, prior to initiation of study treatment) included as covariates.

Attrition/Missing Data: Even though returning a baseline CGM sensor (i.e. the one placed during the run-in phase) is one of the trial eligibility criteria, some participants may not complete the entire follow-up period, or may have missing data for part of the intensive CGM monitoring phase (e.g. they may have usable data for one or more sensors, while one or more sensors may be lost or unusable). If a

participant has missing CGM data during the intensive CGM monitoring period, their values for the primary and secondary CGM-related outcomes will be computed based on the sensors that they have returned with usable data during the follow-up phase. If a participant discontinues before any of the follow-up CGM data are recorded (e.g. participant has no recorded CGM data at all during follow-up) they will be excluded from the primary analysis. As described above, we are planning the study to have sufficient power with a usable analytic sample of n=300 participants. We propose to recruit n=400 participants, which allows for up to 25% attrition (participants that are lost shortly after randomization, before any CGM data have been collected) while retaining sufficient power to test our primary hypothesis.

Missing Data: In recognition of the fact that in some cases a participant's discontinuation could represent a negative clinical outcome, we will perform several sensitivity analyses to ensure that we are thorough and transparent in reporting the possible effects that the missingness would have on our primary analysis. The first sensitivity analysis will be multiple imputation analysis, imputing the missing outcome data based on observed baseline data; this approach is preferred to single-imputation (e.g. last observation carried forward or assign-the-worst) as it takes into account residual uncertainty in the missing values. The second sensitivity analysis will be a win-ratio analysis where participants that died during the study are ranked as having the worst possible outcome; participants that discontinued study participation due to an adverse event are ranked as having the second worst outcome value; participants that discontinued with no known adverse event are ranked as having the third worst outcome value; and participants that return complete CGM data during the intensive follow-up period are ranked according to their % time-in-serious-hypoglycemia (<54 mg/dl), with higher scores representing worse outcomes. This approach provides an estimate of which treatment arm led to better overall outcomes while including death, discontinuation, and hypoglycemia into a single composite outcome measure. This will not be the primary analysis due in part to difficulty interpreting the results and the emphasis on glycemic control as the most important outcome in this therapeutic trial, but it will provide an important check that any observed benefits on a time-in-serious-hypoglycemia outcome or the time-in-range outcome are not offset or explained by greater death or discontinuation in the other treatment arm.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary outcomes are: Time-in-hypoglycemia (<70mg/dl), time-above-range (either >180mg/dl or >250mg/dl), and number nocturnal hypoglycemic events (1200-0600h). We will also measure and compare overall glycemic control (HbA1c), the rate of severe hypoglycemic events (requiring the external assistance of another party), and the rate of symptomatic hypoglycemic events reported by clinical history, rate of diabetic ketoacidosis (measured by self-report and confirmed through review of hospital records) and overall mortality (all cause death).

We will also measure and compare quality of life using validated tools (PedsQL v3 and Insulin Treatment Satisfaction Questionnaire) at baseline and at 6 and 12 months after randomization. A minimum clinically important difference in QoL scores will be determined *a priori*. The primary treatment comparison for QoL will be made between the two treatment arms at 6 months after randomization.

9.4.4 SAFETY ANALYSES

See primary outcome and statistical analysis plan (9.4.2). We anticipate that hypoglycemia will be one of the most frequently occurring safety endpoints.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline Characteristic	Glargine	Usual care Human Insulin
Age		
7-10		
10-14		
15-25		
Male sex		
Race		
Asian		
African		
Other		
Country		
Bangladesh		
Tanzania		
Iraq		
Other		
Duration of type 1 diabetes, years, mean [SD]		
Comorbidities		
Retinopathy		
Nephropathy		
Diabetic foot disease		
HbA1c (%), mean [SD]		
Insulin Regimen		
NPH + regular		
Premixed 70/30		
Premixed 70/30 + regular		
Other		
Baseline insulin dose, IU per kg, mean [SD]		
Total		
Basal		
# of hypoglycemic events in past month, mean [SD]		
Hypoglycemic unawareness		
c-peptide level, ng/ml, mean[SD]		

9.4.6 PLANNED INTERIM ANALYSES

There will be no planned interim analyses testing for efficacy or futility; by the time a sufficient amount of patients have completed follow-up to perform such analyses the trial should be almost fully enrolled. Data on enrollment, progress during the trial, and safety will be reported to the DSMB every 6 months during the study so they may monitor for any safety concerns. There are no pre-specified stopping triggers, but the DSMB has leeway to recommend a pause in enrollment if they judge a preponderance of safety events in one arm to warrant closer examination.

9.4.7 SUB-GROUP ANALYSES

In recognition of the possibility that treatment effect may vary according to select baseline factors that may influence our clinical outcomes, we will include several planned subgroup analyses. The most important of these will be the patient's insulin prior to randomization (NPH versus 70/30), which allows an unbiased comparison of the glargine versus NPH and the glargine versus 70/30, though admittedly these comparisons will be underpowered. In addition, we will examine whether the treatment effect differs by clinical site (Bangladesh, Tanzania or Iraq) and when comparing the route of insulin delivery (pens versus syringe and vial). The principal goal of these subgroup analyses will be to check for apparent consistency in the treatment effect of analogue against both potential options within the usual care group. We will also perform subgroup analyses by age groups (e.g. younger vs older children/youth), and baseline hypoglycemia risk.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not Applicable.

9.4.9 EXPLORATORY ANALYSES

Some sites (e.g. MSF Iraq) may collect data on adults over the age of 25 who meet the inclusion and exclusion criteria for this trial (mainly pediatric and youth populations). The data collected on these participants will not be analyzed in this trial.

However, data from that population may be used in an ancillary study to look at hypoglycemia risk and glycemic control comparing human versus analogue insulin among adults with type 1 living in lower resource or humanitarian settings. Power in that ancillary study may vary depending on the primary outcome selected and the exact study design. If deliberately underpowered, the data collected from that population will be considered pilot or exploratory; to help inform the design of a follow-on, adequately powered trial.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol (see approved consent from from Pitt IRB).

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funder, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

To protect the identity of the participant, unique identifiers (e.g. name, address) will be removed prior to any data being transmitted to the investigators at the University of Pittsburgh. Study participants will be assigned a unique Study ID number. The key or crosswalk file that converts a scrambled Study ID number to a patient medical record number (i.e. re-identification) will only be available to local study staff. The University of Pittsburgh study staff will not have access to these key(s).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not Applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

The Pitt PI (Dr. Luo) will interact with the local study team through virtual meetings (Zoom calls) occurring at least once per month. During these meetings, the study team will monitor participant

enrollment, baseline characteristics, insulin titration, completion of follow-up visits and CGM sensor data collection, withdrawals, and adverse events.

We will establish an independent data safety monitoring committee that will meet once every 6 months to go over interim study findings and reports. The committee will be comprised of experts from outside of the study team and sponsor and will ideally include someone living with type 1 diabetes. For example, it may include a pediatric endocrinologist from UPMC or an academic pediatric endocrinologist or diabetes researcher from outside of PItt/UPMC. It will also include an outside statistician. They will be tasked with assessing the risks and benefits to study subjects and the chair will be empowered to contact the IRB and sponsor independently if it is determined that the trial should be stopped or modified.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the PI, co-Is and site PIs.
- On-site visits once per year
- Virtual calls once per month
- Regular review of data, at least every 6 months (including enrollment, outcome/safety assessments, loss to follow-up, missing data and other key data variables).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Standardized in-person training on study procedures and data collection steps will be provided to all staff involved in data collection. Staff will receive refresher training remotely. The quality of the data collected will be periodically assessed centrally by the Data Center to ensure that they are free of data entry errors, missing, or nonsensical results. The periodic assessment will occur both within and across trial sites. Reports will be generated (see data management system section below) and reviewed at least once every 6 months to ensure high quality data and internal trial validity.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

We will develop a web-based online electronic data management system for this trial. The system (accessible from any computer with internet access) guides study staff through our recruitment and informed consent procedures, study interventions and handles the randomization of study participants. The electronic system will be also used to securely record and transmit trial data (endpoints, safety events) from local sites to the Data Center at the University of Pittsburgh. The system is pre-programmed with skip patterns, drop-down menus, check-off boxes, and other error checking routines that monitor forms for out-of-range values and missing data.

10.1.9.2 STUDY RECORDS RETENTION

Study records should be retained for a minimum of 2 years after the patient last visit. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the PI. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

Date of Violation (Month/Day/Year)	
Enrollment of an ineligible participant	
Failure to collect informed consent/assent	
Failure to collect baseline surveys or lab results (e.g. HbA1c)	
Failure to place or collect baseline CGM sensor data during run-in phase	
Randomization of an ineligible participant (or participant who did not complete all stages of run-in phase)	
Missed clinic visit	
Missed home visit for CGM sensor replacement	
CGM sensor error or failure to download sensor data	
Participant failed to titrate insulin during 4 week titration period	
Participant discontinued study medication	
Cross-over of insulin (i.e. A→H or H→A)	
Failure to collect follow-up HbA1c	
Failure to replace or collect follow-up CGM sensor data	
Breach of confidentiality	
Participant lost to follow-up	
Participant withdrew from study	

Participant began using any non-study CGM device	
Participant used rescue medication, intranasal glucagon: provide date of use and what actions were taken	
Other	
Is the participant eligible to continue on study? (Yes or No)	

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting the PI. Individual de-identified data may be made available in a public repository if consent has been obtained from study participants.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the University of Pittsburgh has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

No interaction with human subjects will occur until after IRB/ethical approval by both the University of Pittsburgh and local IRBs.

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer's IB, package insert, and device labeling.

Examples:

- ***Journal citation***
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
- ***Whole book citation***
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- ***Chapter in a book citation***
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
- ***Web Site citation***
  Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
- ***Electronic Mail citation***
  Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- ***References to package insert, device labeling or investigational brochure***
  Cite date accessed, version number, and source of product information.